REMARKS

Claims 1, 4-20 are pending. Claims 1, 7 and 13 have been amended and 15-20 have been added. Claims 2-3 have been cancelled. No new matter has been added by way of amendment.

Claim Rejections under 35 U.S.C. §112

The Examiner rejected claims 1-14 under 35 U.S.C. 112 on the assertion that the specification does not reasonably provide the enablement for prevention of heart failure. While the applicant does not agree with the Examiners position applicant has deleted this phrase from the subject claims in order to facilitate action in the application. Applicant reserves the right to pursue this subject matter in divisional/continuation applications.

Claim Rejection under 35 USC §103

The Examiner rejected claims 1 and 3-4 under 35 U.S.C. 103(a) as being unpatentable over Psiorz et al in combination with Rieu et al, the Merck Manual, Hodges et al. Kleeman and Liu each cited therein. The Examiner asserts that the Merck Manual, Bergeron and Hodges teach that arrythmias are associated with heart failure and that since Psiorz teaches that Cilobradine lowers heart rate and Rieu teaches that Cilobradine has no negative inotrophic or hypotensive effect, it would have been obvious to use Cilobradine in a method of treating heart failure and also in use with other therapeutic agents for treating heart failure since the other therapeutic agents are known to be used for the same purpose as disclosed in the prior art.

Applicant respectfully disagree with the Examiner that Psiorz et al alone or in combination with any other prior art reference teaches or suggests the claimed methods.

The instant claims are directed to a method for the treatment of heart failure, which comprises the administration to a patient in need thereof of a pharmaceutical composition comprising Cilobradine or a pharmaceutically acceptable salt thereof, together with a pharmaceutically suitable carrier. Psiorz et al discloses Cilobradine as a cardioactive substance which reduces heart rate and has the effect of reducing the oxygen requirement of the heart. Psiorz, however fails to teach the use of Cilobradine to treat heart failure. None of the references: Rieu et al, The

Merck Manual, Bergeron and Hodges et al, fill the gap between Psiorz et al and the instant claims. The Merck Manual which the Office relies on to establish a prima facie case, mentions that the "clinical manifestations of hypertrophic cardiomyopathies (HCM) are chest pain, syncope, palpitations, effort dyspnea, sudden death, alone or in combination". However, none of these clinical signs, alone or in combination, are disclosed in any other references cited by the Examiner in connection with Cilobradine. For the sake of completeness, the Merck Manual additionally teaches that the above mentioned clinical manifestations can exist either alone or in any combination. The Merck manual also states that the most common *prognosis* of HCM is chronic heart failure and sudden death, sudden death being the most common *prognosis* followed by chronic heart failure occurring less often (page 521, lines 23 and 24). As far as the treatment of diseases is concerned, the Merck manual only gives information on the treatment of HCM and not heart failure. Furthermore, the Merck Manual teaches that ß-Adrenoceptor blockers and Ca-channel blockers, alone or in combination, are the mainstay of treatment through their abilitiy to decrease myocardial contractility (page 521, lines 27 – 37). Slowing the heart rate is seen as an added benefit of ß-Blockers, not as a treatment therapy. Monotherapy of HCM with Ca-channel blockers is equally promoted (" ... ß-Adrenoceptor blockers and Ca-channel blockers, ***alone*** *or in combination*, ...). Once diagnosed, the mainstay of therapy disclosed by the Merck manual are ß-Adrenoceptor blockers and Ca-channel blockers, alone or in combination (The Merck manual). Thus, the reference clearly fails to teach or disclose cilobradine for the *treatment* of heart failure (i.e. even if heart failure is cited there as a possible prognosis of HCM, the Merck reference does not teach or suggest the use of cilobradine for the treatment of heart failure as such).

Rieu discloses a class a compounds possessing full specific negative chronotropic activity, these compounds include Cilobradine and Zatebradine. Rieu then discusses that protective effects have been shown in angina with Alinidine, Falipamil and Zatebradine, and suggests a therapeutic potential in the treatment of chronic stable angina and heart failure for these three compounds.(see col. 1, line 17-19.) Rieu, therefore fails to teach or suggest that Cilobradine specifically is useful to treat heart failure. This also renders moot the rejection with respect to the other secondary references Bergeron and Hodges et al. Thus, at the time of the filing of the invention Cilibradine was not known for anything else than for its long lasting heart

rate reducing activity and its effect of reducing the O2 requirements of the heart (from Psiorz et al.), or for its full specific negative chronotropic activity devoid of negative inotropic effects and hypotension (from Rieu et al.). Furthermore, the rationale for the treatment of heart failure with Cilobradine (see page 1 to 10 of the description), and the advantages of Cilobradine with respect to the other known treatments, especially as shown with a comparison with Zatebradine (Fig. 1 in the specification), differentiate the use of Cilobradine for the treatment of heart failure form that of already known treatments.

Applicants therefore content that without improperly using their disclosure as a roadmap, the links between using Cilobradine as disclosed in Psiorz and Rieu, the Merck Manual, Hodges et al. Kleeman and Liu and it's use to treat heart failure cannot be established.

Double Patenting

The Examiner rejected claims 1 and 3-14 under the doctrine of obviousness-type double patenting over claims 10 and 14 of co-pending Application No. 10/257,481 ('481). Claim 1 of the co-pending '481 application is drawn to a method of treating myocardial diseases accompanied by hypertrophy comprising administering a composition comprising bradycardiac substances. Dependent claim 14 is drawn to the method of claim 10 wherein the composition further comprises specific classes of cardio active substances. The applicant respectfully disagrees with the Examiner's assertion that there is no patentable distinction between the claims of the '481 patent application and the instant claims. In applicant's view the Examiner's rejection is improperly based on the premise that heart failure is a clinical manifestation of myocardial disease accompanied by hypertrophy. As explained above, the instant claims are directed to a method for the treatment of heart failure, which comprises the administration to a patient in need thereof of a pharmaceutical composition comprising Cilobradine. The claims of the co-pending application are by contrast directed to a method for treating myocardial disease accompanied by hypertrophy. Myocardial disease is not the same as heart failure. While the Merck Manual discloses that a prognosis of hypertrophic cardiomyopathy may be heart failure the prognosis is clearly distinguishable from the disease condition. Therefore, the instant claims and the claims of the '481 application are patentably distinct.

Applicants respectfully submit that all of the subject claims are in the condition for allowance. If the Examiner feels that a telephone interview would be helpful in advancing prosecution of this application, the Examiner is invited to contact the attorney below.

Respectfully submitted,

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